Medical and Pediatric Oncology 29:157–166 (1997)

Contemporary Classification of Histiocytic Disorders

Blaise E. Favara, MD,* and Alfred C. Feller, MD, with members of the WHO Committee on Histiocytic/Reticulum Cell Proliferations: Macro Pauli, MD, Elaine S. Jaffe, MD, and Lawrence M. Weiss, MD, and for the Reclassification Working Group of the Histiocyte Society: Maurizio Arico, MD, Peter Bucsky, MD, R. Maarten Egeler, MD, Goran Elinder, MD, Helmut Gadner, MD, Mary Gresik, MD, Jan-Inge Henter, MD, Shinsaku Imashuku, MD, Gritta Janka-Schaub, MD, Ron Jaffe, MD, Stephan Ladisch, MD, Christian Nezelof, MD, and Jon Pritchard, MD

Pathologists and pediatric hematologist/oncologists of the World Health Organization's Committee on Histiocytic/Reticulum Cell Proliferations and the Reclassification Working Group of the Histiocyte Society present a classification of the histiocytic disorders that primarily affect children. Nosology, based on the lineage of lesional cells and biological behavior, is related to the ontogeny of histiocytes (macrophages and dendritic cells of the immune system).

Dendritic cell-related disorders of varied biological behavior are dominated by Langerhans cell histiocytosis, but separate secondary proliferations of dendritic cells must be differentiated. Juvenile xanthogranuloma represents a disorder of dermal dendrocytes, another dendritic cell of skin. The hemophagocytic syndromes are the most common of the macrophage-related disorders of varied biological behavior.

Guidelines for distinguishing the exceedingly rare malignant diseases of histiocytes from large cell lymphomas through the use of a battery of special studies are provided. Med. Pediatr. Oncol. 29:157–166, 1997.

Key words: histiocytosis; histiocytic neoplasms; Langerhans cell histiocytosis; hemophagocytic syndrome; histiocytes

INTRODUCTION

Although the histiocytic disorders considered here are rare, their occurrence, most often in children, frequently presents significant diagnostic challenges and only vague notions of nosological context. Since its inception in 1985, the Histiocyte Society has been active in studying these diseases and in clarifying a confusing literature. It is gratifying to see the classification and diagnostic criteria published in 1987 become recognized as the standards in the field [1]. In that publication it was noted, however, that ''The recommended nomenclature and criteria, based on current knowledge, are clearly open to change.'' Information, since acquired and summarized in Table I, justified reassessment in a joint undertaking by pathologists and pediatric hematologist/oncologists of the World Health Organization's Committee on Histiocytic/Reticulum Cell Proliferations and the Reclassification Working Group of the Histiocyte Society.

The clinicopathological taxonomy, diagnostic strategies and related commentary presented here reflect consensus opinions of workers in the field who collectively have studied what is estimated to be over 1,500 cases of histiocytic disorders in the past 10 years. This extraordinary composite experience is, in part, attributed to unprecedented international collaboration. It is not intended that the classification scheme be all encompassing or that this treatise be encyclopedic; instead, it is meant to provide a practical categorization of several related diseases, views on histogenesis and aides to diagnosis. Only the most prevalent of these uncommon maladies are considered and we focus on those that are either prone to systemic involvement or those that must be differentiated from systemic diseases. Some of the vast array of dermatological lesions that feature histiocytes and that are identified by the presence or absence of the MS-1 high molecular weight protein are not included [10]. The list of disorders shown in Table II is cell lineage-oriented with indications of biological behavior. The category ''Disorders of varied biological behavior'' excludes disorders that are considered to be malignant while recognizing a wide scope of severity ranging from self-limited

Contract grant sponsor: Histiocytosis Association of America.

*Correspondence to: Blaise E. Favara, M.D., National Institutes of Health, Rocky Mountain Laboratories, Laboratory of Persistent Viral Diseases, Hamilton, MT 59840-2999.
E-mail: Blaise_Favara@NIH.GOV

Received 17 September 1996; Accepted 29 January 1997

TABLE I. Recent Advances in the Understanding of Histiocytic Disorders

1. Molecular clonality studies have shown that Langerhans cell histiocytosis is a monoclonal disease of varied biological behavior [2], and Rosai-Dorfman disease is a polyclonal disorder [3].
2. Lesions featuring dendritic cells of various types, found in association with lymphomas and pulmonary tumors predominately, have characteristics sufficiently different from Langerhans cell histiocytosis to justify separate consideration.
3. Extraordinarily rare leukemias with phenotypes of dendritic cells have been identified [4,5].
4. The dermal dendrocyte, another accessory dendritic cell, has been demonstrated to be the chief element featured in juvenile xanthogranuloma and related disorders [6].
5. Tumors of follicular dendritic cells and their biology have been defined [7,8].
6. The rarity of malignant disorders that feature histiocytes is clear. Distinction between these histiocytic malignancies and morphologically similar large-cell lymphomas is facilitated by the use of molecular genetic techniques.
7. The results of in vitro studies of hemopoietic stem cells and the influence of cytokines on differentiation have provided important insights into the ontogeny of dendritic cells [9].

*The term histiocytes embraces macrophages and dendritic cells.

TABLE II. A Contemporary Classification of Histiocytic Disorders

- Disorders of varied biological behavior[a]
  - Dendritic cell-related
    - Langerhans cell histiocytosis
    - Secondary dendritic cell processes
    - Juvenile xanthogranuloma and related disorders
    - Solitary histiocytomas of various dendritic cell phenotypes
  - Macrophage-related
    - Hemophagocytic syndromes
      - Primary hemophagocytic lymphohistiocytosis (Familial and sporadic; commonly elicited by viral infections)
      - Secondary hemophagocytic syndromes
        - Infection-associated
        - Malignancy-associated
        - Other
    - Rosai-Dorfman disease (Sinus histiocytosis with massive lymphadenopathy)
    - Solitary histiocytoma with macrophage phenotype
- Malignant Disorders[a]
  - Monocyte-related
    - Leukemias (FAB and revised FAB classifications)
      - Monocytic leukemia M5A and B
      - Acute myelomonocytic leukemia M4
      - Chronic myelomonocytic leukemia
    - Extramedullary monocytic tumor or sarcoma (monocytic counterpart of granulocytic sarcoma)
  - Dendritic cell-related histiocytic sarcoma (localized or disseminated)
    - Specify phenotype; follicular dendritic cell, interdigitating dendritic cell, etc.
  - Macrophage-related histiocytic sarcoma (localized or disseminated)

[a]See text for comments on classification of disorders with aberrant phenotypes.

to lethal disease. These eclectic disorders are unified by the principal pathological cells being histiocytes, but storage diseases, hyperlipidemic xanthomas, well-defined chronic infections such as tuberculosis and leprosy and granulomatous reactions to foreign materials are excluded. We espouse the continued use of the term ''histiocyte,'' even though it continues to be under attack [11], provided it is defined and used consistently. We view histiocytes as a group of immune cells, familiar to morphologists, that includes macrophages and dendritic cells. Macrophages, with predominately antigen processing functions and dendritic cells with primarily accessory cell or antigen presenting functions are best,'' . . . considered as polar representatives of one common regulatory system [12].'' The term ''histiocyte'' can be considered analogous to ''lymphocyte'' in that both denote groups of immune cells that are phenotypically and functionally diverse.

Although the ontogeny of histiocytes is currently incompletely understood, a serviceable panorama is represented in Figure 1. The derivations of follicular dendritic cells and dermal dendrocytes remain controversial. Most evidence indicates that follicular dendritic cells are of mesenchymal (nodal stromal) origin, but a bone marrow source hasn't been excluded [13,14]. Similarly, dermal dendrocytes are thought to develop from cutaneous mesenchymal (fibroblastic) precursors, but a hemopoietic source has also been proposed [15,16]. It is also plausible that both of these dendritic histiocytes follow more than one pathway of development under appropriate cytokine control. GM-CSF seems to be a powerful influence in the development of dendritic cells in general [12,17,18]. Although supporting data are unavailable, it is likely that cells with the potential to acquire characteristics of dendritic cells and those of macrophages are widespread in the body and that, under special conditions, there is local induction of the phenotype most appropriate to meet the demands of the time and place.

Since the nomenclature of dendritic cells is not uniform in the literature, terms used here are specified. The close relationship between Langerhans cells, indeterminate cells of the dermis, and interdigitating dendritic cells of lymph nodes warrants considering them as a family of cells or as a ctyological continuum. The indeterminate cell, which many view as a pre-Langerhans cell that has not acquired Langerhans cell granules [19], is apparently different from the ''indeterminate cell'' of Peters et al. [12], who describe an element with the potential to become either a macrophage or a dendritic cell [12]. We have referred to this pluripotent cell as a ''transitional macrophage/dendritic cell.'' The term ''interdigitating dendritic cell'' is preferred to ''interdigitating reticulum cell'' since it identifies the element as one of immunodendritic type, and it corresponds well with the term ''follicular dendritic cell,'' both being normal residents

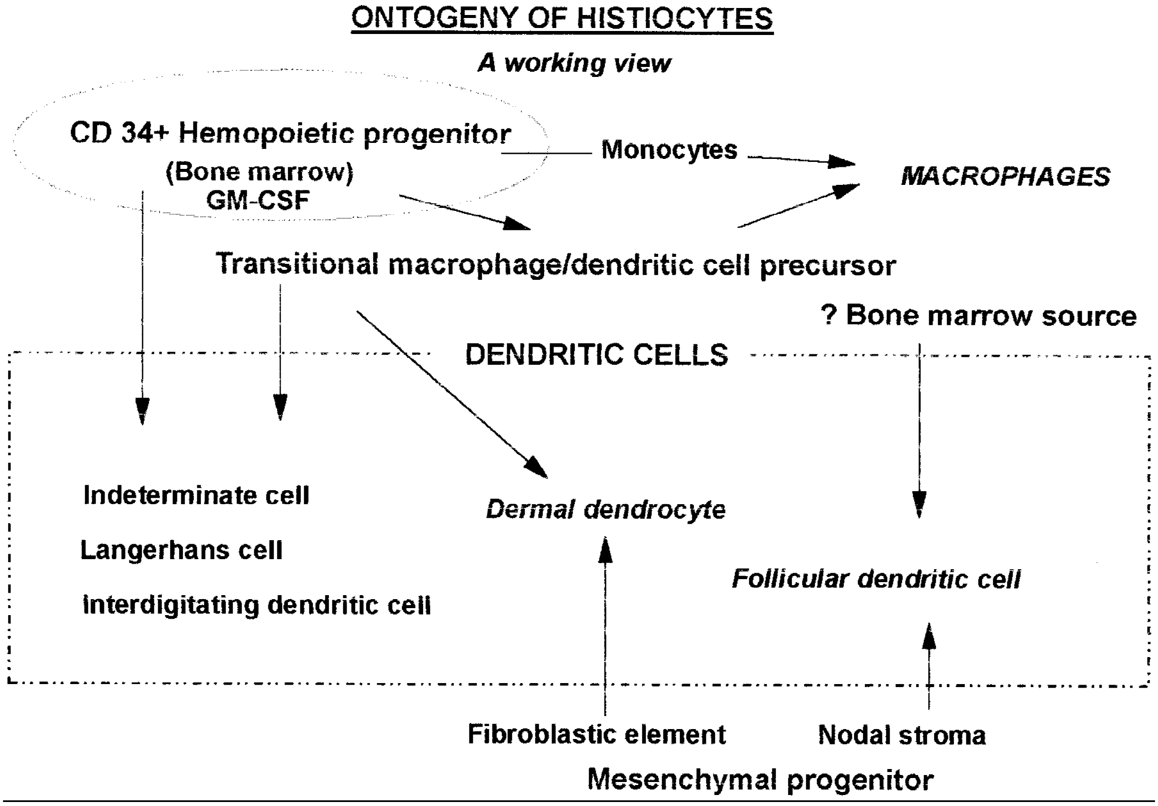

Fig. 1. Much of the basis for this scheme of ontogeny derives from in vitro work in developing systems for the production of dendritic cells for immunotherapy. Cytokines: GM-CSF, TNF alpha, IL-4, etc., play important roles in these pathways and GM-CSF is fundamental to the differentiation of the Langerhans cells [9,12,17,18].

of lymph nodes. The dermal dendrocyte is the factor XIIIa+ dendritic cell that is also referred to as the dermal dendrophage or perivascular dermal dendrocytic cell [15,16]. It is different from the indeterminate cell, another dendritic cell of the dermis.

The intimate relationships between macrophages and dendritic cells result in functional, morphological and phenotypic overlap. Cellular characteristics not only change with stage of development but also under influences of the microenvironment [12,20]. Nonetheless, in a clinical setting, immunophenotyping is useful in separating macrophages, which are characteristically phagocytic cells with prevalent antigen processing functions, from dendritic cells with predominately antigen presenting capabilities. Table III shows identifying features of the various types of histiocytes. Cytomorphology, as displayed in hematoxylin and eosin (H & E) stained sections, provides only soft evidence of lineage. Histiocytes with lobulated, convoluted or grooved nuclei are likely to be dendritic cells, the interdigitating dendritic cell exhibiting this nuclear morphology most strikingly. As more histiocytic lesions are evaluated with batteries of immunohistochemical stains and with other methods, aberrant phenotypes that fit no distinctive pattern are likely to be encountered. The diagnostician must consider the entire profile of the lesional cells, not lose sight of the morphological appearance of H&E stained sections that still provides the underpinnings of diagnostic histopathology, and always consider findings in clinical context. In some instances, a descriptive diagnosis is all that can be justified, such as, ‘‘unclassified histiocytic disorder of uncer-

TABLE III. Identifying Features of Histiocytes

Macrophage	Lysozyme, CD45, CD14 and CD68+. S100[a], CD1a and Factor XIIIa negative. Langerhans cell (Birbeck) granules absent.
Indeterminate cell	CD45, S100 and CD1a+ Factor XIIIa negative. Langerhans cell granules absent.
Langerhans cell	CD45, S100, and CD1a+. CD14 and Factor XIIIa negative. Langerhans cell granules present.
Interdigitating dendritic cell	CD45 and S100+. CD14, CD1a and Factor XIIIa negative. Langerhans cell granules absent.
Dermal dendrocyte	Factor XIIIa, CD45 and CD68+. S100 and CD1a negative. Langerhans cell granules absent.
Follicular dendritic cell	KiM4, CD21, CD35+. S100 variable. CD45 negative. Langerhans cell granules absent.

[a]See text for caution regarding S100 staining.

tain biological behavior,'' followed by a delineation of the phenotype of the lesional cells. A means of cataloging cases with aberrant phenotypes and their clinical behavior is needed to assure that important correlations are recognized.

The classification scheme presented here differs from the Histiocyte Society's 1987 version in several aspects and from that offered more recently by Cline [1,21]. Initially, Langerhans cell histiocytosis (LCH) was thought to be the sole dendritic cell disorder, but maladies have been described in which other dendritic histiocytes: indeterminate cells, interdigitating dendritic cells, dermal dendrocytes and follicular dendritic cells, are the principal elements. The dermal dendrocyte has been established as the key cell in most cases of juvenile xanthogranuloma and related disorders [4]. Diagnostic criteria for LCH have been modified, expanded concepts of the hemophagocytic syndromes are presented, and the diversity of the challenges presented by the rare malignant disorders are addressed.

Langerhans Cell Histiocytosis (LCH)

Terms that are viewed as obsolete or unnecessary but synonymous with LCH include: histiocytosis X, eosinophilic granuloma, Letterer-Siwe disease, Hand-Schuller-Christian syndrome, Hashimoto Pritzker syndrome, self-healing histiocytosis, pure cutaneous histiocytosis, Langerhans cell granulomatosis, Langerhans cell (eosinophilic) granulomatosis, type II histiocytosis and nonlipid reticuloendotheliosis. The use of strict criteria for a definitive diagnosis of LCH, as published in 1987 [1], has assured validity and standardization of the diagnosis; characteristic conventional morphology of LCH must be wed to evidence that at least some of the lesional histiocytes have the Langerhans cell phenotype. The Langerhans cell (Birbeck) granule is the only specific property of this phenotype. The CD1a surface antigen is a convenient but less specific marker having been described in histiocytic disorders other than LCH such as rare cases of deep-seated juvenile xanthogranuloma [22] and Rosai-Dorfman disease [3].

The introduction of antibody 010 that detects the CD1a antigen in routinely processed paraffin-embedded specimens promises to be valuable and will alleviate the need for other ancillary stains [23]. More experience with this antibody should clarify its specificity, its sensitivity having been shown to be adequate for diagnostic purposes [24]. Requirements for a definitive diagnosis of LCH remain unchanged. The demonstration of the Langerhans cell granule by electron microscopy remains the ''gold standard'' of the phenotype, but exhibition of the CD1a antigen on lesional cells also provides the basis for a definitive diagnosis using conventional antibodies to the CD1a antigen in frozen sections or the 010 monoclonal antibody in paraffin sections.

Initially, the next level of less diagnostic confidence (stated simply as ''diagnosis'') required the demonstration of two or more nonspecific but characteristic markers of the Langerhans cell phenotype. The availability of the antibody 010 makes this diagnostic tier redundant; it has been omitted. Only a ''presumptive diagnosis'' of LCH can be justified on the basis of conventional histology alone. A definitive diagnosis and a presumptive diagnosis thus reflect the two levels of confidence in the diagnosis of LCH.

Although not a diagnostic marker, S-100 is commonly used and remains useful in the evaluation of histiocytic disorders. A positive stain indicates that the lesional histiocytes are likely to be either Langerhans cells, indeterminate cells, or interdigitating dendritic cells, but additional confirmatory studies (EM and/or CD1a) are required for a confident diagnosis of LCH. It must also be appreciated that some histiocytes other than these dendritic histiocytes may also be S100+. The characteristic histiocyte in Rosai-Dorfman disease, activated macrophages in reactive lymph nodes and macrophages in some cases of hemophagocytic syndrome, are S100+. Cells other than histiocytes that are also S100+ include neval cells and chondrocytes.

The clinical stratification of cases of LCH based on extent of disease is an influential factor in therapeutic decisions. The Histiocyte Society's Treatment Protocol for Langerhans cell histiocytosis categorizes patients as those with single-system disease involving a single site, those with single-system disease affecting multiple sites, and those with multisystem disease [25]. Among those with multisystem disease, particularly infants, there is still a mortality rate that warrants aggressive therapy. The absence of mortality in the large series of cases reported by Lieberman et al. [11] is unique and unexplained. Isolated pulmonary Langerhans cell disease of adults is an affliction that is sufficiently different from LCH to warrant being considered as an LCH variant [26]. It is essentially a smoker's malady confined to the lungs, where it progresses indolently to fibrosis in many cases, and there is a strong association with malignancies. This form of lung disease is exceedingly rare in children, who may have severe and even lethal pulmonary involvement as an acute manifestation of multisystem disease but usually without progressive fibrosis.

Characteristics of LCH lesions have been further elucidated. Lesional cells show proliferation indices, based upon the expression of the proliferating cells nuclear antigen, ranging from 3% to 48% with the largest indices being observed in lesions of lymph nodes [27, 28]. Proliferative indices have not been proven to be prognostic.

Langerhans cell histiocytosis has been shown to be a monoclonal proliferation of CD1+ histiocytes in all forms of disease: in the banal solitary lytic lesion of bone, in disseminated multisystem disease of infancy that

carries a significant mortality rate and in the intermediate form of disease that usually has multisystem involvement and chronic course [2,29]. Clonality has, therefore, not proven to be prognostic in LCH. Clonality studies in the pulmonary disease of smokers have not been published. Although monoclonal proliferations of hemopoietic cells are usually neoplastic, the pathobiological significance of monoclonality in LCH is still unclear. More data are needed including those concerning multiple and recurrent lesions in the same patient and the clonality of normal epidermal Langerhans cells. Attempts at cytogenetic studies have usually failed since lesional cells do not propagate in culture and direct preparations have not been rewarding in spite of high proliferative rates in some lesions. No evidence of somatic mutation has been found in the lesions of LCH using comparative genomic hybridization [30]. The use of growth factors in tissue cultures of material from lesions of LCH holds promise of more critical cytogenetic and molecular genetic information.

Although several studies have failed to define a role for viruses in the pathogenesis of LCH, the possibility remains. The presence of human herpesvirus type 6 genome in LCH lesional tissue was not confirmed [31,32]. The conceivable role of a superantigen in the pathogenesis of LCH is under investigation [33]. Characterization of adhesion molecules in the disease, in secondary dendritic cell processes (considered below) and in normal Langerhans cells has provided interesting but not definitive insights [34]. An animal model of this disease and means of establishing cell lines from lesions are badly needed. A histiocytic disorder of the Bernese mountain dog is a leading candidate for a model of this enigmatic disease [35].

Secondary Dendritic Cell Processes

Not all lesions that feature collections of dendritic cells, including Langerhans cells, fall into the clinco-pathological spectrum of LCH. Accumulations of dendritic cells, most often Langerhans cells, are uncommonly encountered in diagnostic material that features primary diagnoses of lymphoma, lung, thyroid and other tumors [36]. Secondary dendritic cell processes featuring Langerhans cells and occasionally interdigitating dendritic cell lesions are most frequently seen in lymph nodes of patients with Hodgkin's disease. When these lesions feature cells with the Langerhans cell phenotype, they may be histologically identical to those of LCH and distinction requires informed clinical correlation. In the case of secondary dendritic cell processes associated with lung tumors, the scenario seems be a regional one mediated by cytokines that favor induction of the Langerhans cell phenotype in local cells [32]. Proliferations of follicular dendritic cells associated with lymphomas are thought to have diagnostic and prognostic relevance [38,39]. The secondary dendritic cell processes usually involute as the associated principal disease is controlled. Clonality studies of cells from these lesions have not been reported.

Juvenile Xanthogranuloma

Juvenile xanthogranuloma (JXG) is the histiocytic disorder most often misdiagnosed as LCH. Since all but the rarest lesions of JXG, including the few that are extracutaneous [40], involute spontaneously, it is therefore imperative that this disease be recognized to avoid unnecessary studies and excessive treatment.

Dermal dendrocytes, normally present in the perivascular area of the papillary dermis, have a phenotype distinct from that of indeterminate cell and Langerhans cell [41]. Although the origin and function of dermal dendrocytes have not been fully defined, these cells constitute the principal element in JXG, xanthoma disseminatum, benign cephalic histiocytosis, progressive nodular histiocytosis, spindle cell xanthogranuloma, and generalized eruptive histiocytosis, disorders that may represent a spectrum of disease rather than entities [6]. Some lesions of juvenile xanthogranuloma are, however, Factor XIIIa negative and seem to be composed of macrophages. The biological significance of this distinction is unclear. More than chance associations between JXG and LCH are suggested by unusual cases of LCH that have coexisting lesions with JXG morphology in the brain and skin, but there are insufficient data to warrant more than speculation on an ontogenetic basis [42].

Solitary Histiocytomas With Dendritic Cell Phenotypes

Tumoral lesions other than those of JXG and LCH, that are composed of dendritic cells without malignant features, may defy precise categorization. Some have the phenotype of the indeterminate cell or that of the interdigitating dendritic cell, and still others have aberrant phenotypes only suggesting a dendritic cell lineage. Although most often cutaneous, these lesions have been seen in the central nervous system as well. These tumors may pose special problems in classification and prediction of behavior. The diagnosis must take into account clinical information regarding the location of the lesion and, most importantly, associated signs of systemic disease. Careful follow-up of patients with dendritic cell histiocytomas is imperative since these lesions may be forerunners of more widespread and serious histiocytic processes.

Hemophagocytic Syndromes

Among the macrophage-related histiocytic disorders, the hemophagocytic syndromes or macrophage activation syndromes are the most prevalent and significant in terms of morbidity and mortality. Diagnostic criteria

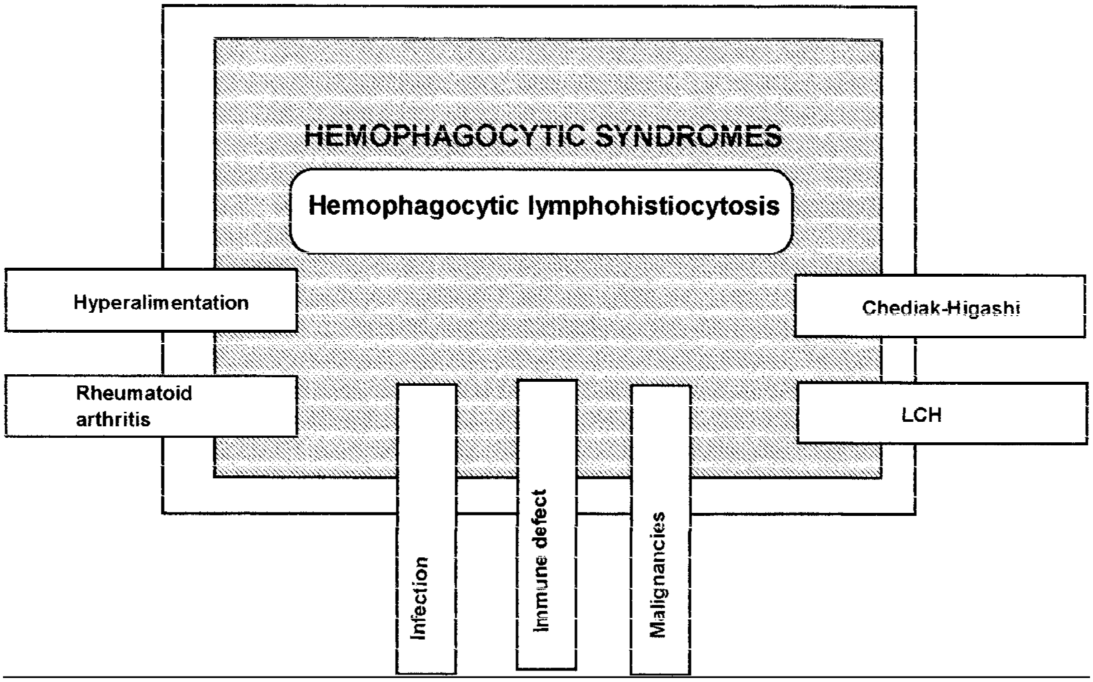

Fig. 2. Hemophagocytic lymphohistiocytosis is the prototype of the hemophagocytic syndrome. Other disorders may manifest a secondary hemophagocytic syndrome during the course of the primary disease; e.g., a patient with a primary, congenital immunodeficiency disorder may develop a hemophagocytic syndrome as a complication of the basic process.

have been defined for primary hemophagocytic lymphohistiocytosis, the prototypical hemophagocytic syndrome, and an international case registry has been established [43,44]. The significance of hemophagocytosis, a relatively common cytomorphological finding in bone marrow and other biopsy specimens, must be considered carefully. Hemophagocytosis alone is not diagnostic of a hemophagocytic syndrome; complementary clinical and laboratory data are required [45]. Diagnostic criteria, defined by the Histiocyte Society, are: fever of otherwise undetermined etiology, splenomegaly, cytopenias, hypofibrinogenemia or hypertriglyceridemia and hemophagocytosis displayed in bone marrow, spleen, lymph node or other tissue. A characteristic liver pathology has important diagnostic implications [46]. These clinical and pathological events of the hemophagocytic syndromes indicate widespread and poorly controlled activation of macrophages with hypercytokinemia [47].

The familial form of primary hemophagocytic lymphohistiocytosis is the prototypic hemophagocytic syndrome. This disease may occur in an obvious familial setting, or it may present as an apparently sporadic event in an only child or in a first-affected child in a family with the putative recessive gene. No means of identifying the gene or its product have yet been reported. It is essential to realize that signs of the primary disorder are often elicited by viral infections, a relationship that compounds the difficulty in distinguishing primary hemophagocytic lymphohistiocytosis, which is lethal without bone marrow transplantation, from a secondary infection-associated disorder in which this treatment may is not be needed.

Infections, particularly viral infections, and malignant disorders (most commonly T-cell lymphomas), can be associated with a secondary hemophagocytic syndrome, especially in the immunocompromised host. The full-blown disorder may also become manifest in other settings: during the course of Chediak-Higashi disease, in rare patients with rheumatoid arthritis, in the extraordinary patient with LCH and during lipid-rich parenteral alimentation, for example [48,49]. Japanese publications have also linked hemophagocytic syndromes with necrotizing lymphadenitis [50]. Some of these relationships are schematized in Figure 2.

Incomplete forms of the hemophagocytic syndrome are probably much more frequent than the complete form described here. These disorders may ultimately be shown to result from defects in lymphocytes, the histiocyte being only a secondary responder. The Histiocyte Society's treatment protocol for hemophagocytic lymphohistiocytosis aims to improve the results of treatment of the highly lethal primary disorder, but some cases of the secondary forms of disease may require at least short-term chemotherapy to control the hemophagocytic syndrome [51].

Rosai-Dorfman Disease

Sinus histiocytosis with massive lymphadenopathy (SHML) or Rosai-Dorfman disease is a polyclonal histiocytic disorder of uncertain etiology [3,52]. The prominence of extranodal lesions and sundry manifestations in a significant number of cases declare the narrowness of the term SHML [53]. The characteristic cell of Rosai-Dorfman disease is of unknown origin but its cytology and phenotype align it most closely with an activated macrophage [3]. On the other hand, the cells are characteristically S100+ express catepsins and uncommonly the CD1a antigen as do Langerhans cells, indeterminate cells and interdigitating dendritic cells. They do not, however, bear the Langerhans cell granule [54].

Malignant Disorders

Malignant diseases featuring monocytes are included since these elements are considered to be precursors of histiocytes. Clearly the monocyte-related malignancies, leukemias for the most part, are the most common of those considered here. Among the various leukemias, those featuring monocytes and monoblasts are the most likely to present with extramedullary tumors or sarcomas [55].

Malignant disorders of histiocytes are extraordinarily rare with less than seven cases/year reported in the literature [56]. It is time to eliminate the term ‘‘true histiocytic lymphoma.’’ Its use only compounds confusion related to the differential diagnosis of hemopoietic neoplasms. The term, ‘‘histiocytic sarcoma,’’ is used here to designate malignant tumors composed of macrophages or dendritic cells [56,57]. It is conceded, however, that use of this term is likely to inspire controversy since some view sarcomas as being only tumors of connective tissue histogenesis; indeed, the biological behavior of histiocytic sarcomas, other than those that feature follicular dendritic cells, resembles that of lymphomas more than that of soft tissue sarcomas. Histiocytic sarcoma can be viewed as a term analogous to the antiquated expression ‘‘lymphosarcoma,’’ which was used to denote malignant tumors composed of lymphocytes, now lymphomas. We have used the designations ‘‘localized’’ and ‘‘disseminated’’ when describing malignant histiocytic disorders of macrophages and dendritic cells. Disseminated disease is equivalent to malignant histiocytosis, a term we have otherwise avoided. As the result of extensive phenotyping of leukemia cells, cases of dendritic cell leukemia have also been characterized [4,5].

The case in which a histiocytic malignancy is suspected can pose significant diagnostic difficulties and at least two challenges: proving the disorder to be malignant and establishing that the malignant cell is a histiocyte. It is perhaps not possible to precisely define malignancy in a way acceptable to all, but certain clinicopathological features may assist in recognizing a disease as being malignant: (1) clonal cytogenetic abnormality, perhaps the most compelling of all, (2) aneuploid DNA ploidy profile, (3) ‘‘malignant’’ histo/cytomorphology, (4) tumorigenicity in animals, (5) monoclonality, (6) high proliferative rate, and (7) characteristic clinical course. All traits are not required and none is independently sufficient to identify a process as malignant.

TABLE IV. Markers of Histiocytes in Malignant Lesions

Positive reactions	
‘‘Most specific’’	“Less specific”
M-CSF receptor	MAC-387
Lysozyme	CD11c
Ki-M8	CD14
S100+ large cells	CD68
Ki-M4	LN5
Cathespin D and E	
CD21	
CD35	

Significant negative findings favoring lymphoid lineage
T-cell receptor and/or immunoglobulin gene rearrangement
Karyotype of large cell anaplastic lymphoma, t[2;5] [p23;q35]
Presence of chimeric protein product $p80^{NPM/ALK}$
Specific T- and B-cell lineage markers (e.g., CD3, CD20, CD79, etc.)

In determining the cell lineage, the major challenge is in distinguishing lymphoid from histiocytic cells. The literature is replete with studies showing that cases once considered to be examples of histiocytic malignancies were actually lymphomas, malignant tumors of lymphocytes [58,59]. Malignancies of natural killer cells may also show morphological features that can be confused with those of histiocytes [60]. Diagnostic criteria for malignant histiocytic tumors have been published [61,62], but Table IV lists markers that may be helpful in defining cells as histiocytes although none are specific and profiles of positive and negative findings are needed to define the cell type. If a lesion features any of the negative findings listed, one must be very cautious in classifying it as histiocytic. On the other hand, if the lesion is lysozyme +, a relatively reliable marker of histiocytes, the burden lies in proving the lesion to be a lymphoma provided that granulocytic sarcoma has been excluded through the use of appropriate markers. The weighted evidence approach suggested by Bucsky et al. [63] should be considered.

Perhaps the most confusing aspect of this field concerns the distinction between large-cell anaplastic lymphoma or anaplastic large-cell lymphoma, an authentic lymphoma, from a tumor of histiocytic origin, a histiocytic sarcoma. If the term lymphoma is reserved for those malignant tumors proven to be of lymphoid cell lineage,

much of this dilemma fades. A tumor with the H&E morphology of large cell anaplastic lymphoma that is also CD30+ requires further study to arrive at a definitive diagnosis, although a CD30+ neoplasm with the morphological features of large cell anaplastic lymphoma is almost always lymphoid in origin. On the other hand, such tumors, when lysozyme+, are likely to be histiocytic with the caveat noted above. Neuroprotein S100 may be a useful marker in context, since S100+ large hemopoietic cells are histiocytes, usually of dendritic lineage. The exception is the histiocyte of Rosai-Dorfman disease but this should not pose an interpretative problem. The rare S100+ lymphomas are small-cell tumors. The presence of the t[2;5][p23;q35]karyotypic abnormality with the 5q35 breakpoint or the presence of its chimeric protein product $p80^{NPM/ALK}$ in a hemopoietic neoplasm weighs heavily in favor of a diagnosis of large cell anaplastic lymphoma or, remotely, Hodgkin's disease or large B-cell lymphoma [64–66]. Although T-cell receptor and immunoglobulin gene rearrangements have also been found in certain nonlymphocytic leukemias, these findings are also powerful indicators of lymphocyte lineage in the setting of lymphocyte-v-histiocyte. When present, these gene rearrangements greatly assist in distinguishing lymphomas from histiocytic and other disorders. Future developments in hematological molecular biology will be important in solving these problems.

All of the disorders considered here are rare, and it is only with effective collaboration and the integration of basic and clinical information that progress will be made in understanding them more fully. As important findings evolve from the abundant basic work on antigen presenting/processing cells, the pathogenesis of the histiocytosis syndromes will undoubtedly be illuminated. Such advances in the field will result in significant benefits to patients with histiocytic disorders and, perhaps, warrant another visit to this area of hematology/hematopathology in the future.

ACKNOWLEDGMENTS

Thanks to Ms. Molly Hackett for critical review of the manuscript.

REFERENCES

1. Writing group of the Histiocyte Society; Histiocytosis syndromes in children. Lancet 1:208–209, 1987.
2. Willman CL, Busque L, Griffith BB, et al.: Langerhans cell histiocytosis (Histiocytosis X): A clonal proliferative disease. New Eng J Med 331:154–160, 1994.
3. Paulli M, Bergamaschi G, Tonon L, et al.: Evidence of a polyclonal nature of the cell infiltrate in sinus histiocytes with massive lymphadenopathy (Rosai-Dorfman disease). Brit J Haematol 91: 415–418, 1995.
4. Srivastava HI, Srivastava A, Srivastava MD: Phenotype, genotype and cytokine production in acute leukemia involving progenitors of dendritic Langerhans' cells. Leukemia Res 18:499–511, 1994.
5. Santiago-Schwarz F, Coppock DL, Hindenburg AA, Kern J: Identification of a malignant counterpart of the monocyte-dendritic cell progenitor in an acute myeloid leukemia. Blood 84:3054–3062, 1994.
6. Zelger B, Cerio R, Orchard G, Wilson-Jones E: Juvenile and adult xanthogranuloma. A histological and immunohistological comparison. Am J Surg Pathol 18:126–135, 1994.
7. Perez-Ordonez B, Erlandson RA, Rosai J: Follicular dendritic cell tumor: Report of 13 additional cases of a distinctive entity. Am J Surg Pathol 20:944–955, 1996.
8. Hollowood K, Stamp G, Zouvani I, Fletcher CDM: Extranodal follicular dendritic cell sarcoma of the gastrointestinal tract. Morphologic, immunohistochemical and ultrastructural analysis of two cases. Am J Clin Pathol 103:90–97, 1995.
9. Caux C, Dezutter-Dambuyant C, Schmitt D, Banchereau J: GM-CSF and TNF-alpha cooperate in the generation of dendritic Langerhans cells. Nature 360:258–261, 1992.
10. Goerdt S, Kolde G, Bonsmann G, Hamann K, Czarnetzki B, Andreesen R, et al.: Immunohistochemical comparison of cutaneous histiocytosis and related skin disorders: Diagnostic and histogenetic relevance of MS-1 high molecular weight protein expression. J Pathol 170:421–427, 1993.
11. Lieberman PH, Jones CR, Steinman RM, et al.: Langerhans cell (eosinophilic) granulomatosis: Clinicopathologic study encompassing 50 years. Am J Surg Pathol 20:519–552, 1996.
12. Peters JH, Gieseler R, Thiele B, Steinbach F: Dendritic cells: From ontogenetic orphans to myelomonocytic descendants. Immunol Today 17:273–278, 1996.
13. Szakal AK, Kapasi ZF, Haley ST, Tew JG: A theory of follicular dendritic cell origin. Curr Top Microbiol Immunol 201:1–13, 1995.
14. Haley ST, Tew JG, Szakal AK: The monoclonal antibody FDC-M1 recognizes possible follicular dendritic cell precursors in the blood and bone marrow. Adv Exp Med Biol 378:289–291, 1995.
15. Pober JS, Sueki H, Murphy GF: MS-1 sinusoidal endothelial antigen is expressed by Factor XIIIa+, HLA-DR+ dermal perivascular dendritic cells. Lab Invest 65:732–741, 1991.
16. Berrutti L, Silverman JS: Cardiac myxoma is rich in factor XIIIa positive dendrophages: immunohistochemical study of four cases. Histopathology 28:529–535, 1996.
17. Szabolcs P, Avigan D, Gezelter S, et al.: Dendritic cells and macrophages can mature independently from a human bone marrow-derived, post-colony-forming unit intermediate. Blood 87:4520–4530, 1996.
18. Caux C, Massacrier C, Dezutter-Dambuyant C, et al.: Human dendritic Langerhans cells generated in vitro from CD34+ progenitors can prime naive CD4+ T cells and process soluble antigen. J Immunol 155:5427–5435, 1995.
19. Murphy GF, Bhan AK, Harrist TJ, Mihm MC: Identification of indeterminate cells in normal human dermis by the use of the monoclonal anti-T6 antibody. Lab Invest 46:60A, 1982.
20. Murphy GF, Messadi D, Fonferko E, Hancock WW: Phenotypic transformation of macrophages to Langerhans cells in the skin. Am J Pathol 123:401–406, 1986.
21. Cline MJ: Histiocytes and histiocytosis. Blood 84:2840–2853, 1994.
22. DeGraaf JH, Timens W, Tamminga RYJ, Molenaar WM: Deep juvenile xanthogranuloma. Hum Pathol 23:905–910, 1992.
23. Krenacs L, Yidzavicz L, Boumsell L: Immunohistochemical detection of CD1a antigen in formalin fixed and paraffin embedded tissue sections with monoclonal antibody 010. J Pathol 171:99–104, 1993.

24. Emile JF, Wechsler J, Brousse N, et al.: Langerhans' cells histiocytosis. Definitive diagnosis with the use of the monoclonal antibody 010 on routinely paraffin-embedded samples. Am J Surg Pathol 19:636–641, 1995.
25. Ladisch S, Gadner H: Treatment of Langerhans cell histiocytosis—Evolution and current approaches. Brit J Cancer 70(Suppl XXIII) S41–S46, 1994.
26. Soler P, Kambouchner M, Valeyre D, Hance AJ: Pulmonary Langerhans' cell granulomatosis (Histiocytosis X). Annu Rev Med 43:105–115, 1992.
27. Hage C, William CL, Favara BE, Isaason P: Langerhans cell histiocytes (Histiocytosis X). Immunophenotype and growth fraction. Hum Pathol 24:840–845, 1993.
28. Favara BE, Steele A: Langerhans cell histiocytosis of lymph nodes: A morphological assessment of forty three biopsies. Ped Pathol Lab Med, 1997, in press.
29. Willman CL: Detection of clonal histiocytes in Langerhans cell histiocytosis: Biology and clinical significance. Br J Cancer 70(Suppl XIII):S29–S33, 1994.
30. Haag MM, Avet-Loiseau H, Favara BE, Steele A, Smith J, Pallavicini MG: Evaluation of a series of cases of Langerhans cell histiocytosis by comparative genomic hybridization. Presented at the 6th International Workshop on Chromosomes in Solid Tumors. Feb 19–21, 1995. Tucson, Arizona.
31. Leahy MA, Krejci SM, Friednash M, et al.: Human herpesvirus 6 is present in lesions of Langerhans cell histiocytosis. J Invest Dermatol 101:642–645, 1993.
32. McClain K, Weiss RA: Viruses and Langerhans cell histiocytosis: Is there a Link? Brit J Cancer 70(Suppl XXIII):S34–36, 1994.
33. Kannourakis GK, Abbas A: The role of cytokines in the pathogenesis of Langerhans cell histiocytosis. Brit J Cancer 70(Suppl XIII):S37–40, 1994.
34. DeGraaf JH, Tamminga RYJ, Kamps WA, Timens W: Expression of cellular adhesion molecules in Langerhans cell histiocytosis and normal Langerhans cells. Am J Pathol 147:1161–1171, 1995.
35. Moore PF, Schrenzel, MD, Affolter VK, Olivry T, Naydan D: Canine cutaneous histiocytoma is an epidermotropic Langerhans cell histiocytosis that expresses CD1 and specific beta 2-integrin molecules. Am J Pathol 148:1699–1708, 1996.
36. Egeler RM, Neglia JP, Arico M, Favara BE, Heitger A, Nesbit ME: Acute leukemia in association with Langerhans cell histiocytosis. Med Ped Oncol 23:81–85, 1994.
37. Colasante A, Castrilli G, Bianca F, Aiello B, Brunetti M, Musiani P: Role of cytokines in distribution and differentiation of dendritic cell/Langerhans' cell lineage in human primary carcinomas of the lung. Human Pathol 26:866–872, 1995.
38. Alavaikko MJ, Blanco G, Aine R, Lehtinen T, Fellbaum C, Taskinen PJ, Sarpola A, Hansmann ML: Follicular dendritic cells have prognostic relevance in Hodgkin's disease. Am J Clin Pathol 101: 761–767, 1994.
39. Leung CY, Ho FC, Srivastava G, Loke Sl, Liu YT, Chan AC: Usefulness of follicular dendritic cell pattern in classification of peripheral T-cell lymphomas. Histopathology 23:433–437, 1993.
40. Freyer DR, Kennedy R, Bostrom BC, Kohut G, Dehner LP: Juvenile xanthogranuloma: forms of systemic disease and their clinical implications. J Pediatr 129:227–237, 1996.
41. Cerio R, Spaull J, Oliver GF: A study of Factor XIIIa and MAC 387 immunolabeling in normal and pathological skin. Am J Dermatol 12:221–233, 1990.
42. Favara BE, Jaffe R: The histopathology of Langerhans cell histiocytosis. Brit J Cancer 70(Suppl XXIII):S17–S23, 1994.
43. Henter J-I, Elinder G, Ost A and the FHL Study Group of the Histiocyte Society: Diagnostic guidelines for hemophagocytic lymphohistiocytosis. Seminar Oncol 18:29–33, 1991.
44. Arico M, Janka G, Fischer A, et al. for the FHL Study Group of the Histiocyte Society: Hemophagocytic lymphohistiocytosis. Report of 122 children from the International Registry. Leukemia 10:197–203, 1996.
45. Favara BE: Hemophagocytic lymphohistiocytosis: A hemophagocytic syndrome. Semin Diagn Pathol 9:63–74, 1992.
46. Favara BE: Histopathology of the liver in histiocytosis syndromes. Ped Pathol & Lab Med 16:413–433, 1996.
47. Fujiwara F, Hibi S, Imashuku S: Hypercytokinemia in hemophagocytic syndrome. Am J Ped Hemat/Oncol 15:92–98, 1993.
48. Stephan JL, Zeller J, Hubert P, Herbelin C, Dayer JM, Prieur AM: Macrophage activation syndrome and rheumatic disease in childhood: A report of four new cases. Clin Exper Rheumatol 11:451–456, 1993.
49. Hesseling PB, Wessels G, Egeler RM, Rossouw DJ: Simultaneous occurrence of viral-associated hemophagocytic syndrome and Langerhans cell histiocytosis. Pediat Hematol/Oncol 12:135–141, 1995.
50. Iijima K, Sugita K, Kojika S, et al.: Recurrent subacute necrotizing lymphadenitis in a girl presenting with hemophagocytic syndrome at second relapse. Jap J Pediat Hematol 10:122–126, 1996.
51. Henter J-I, Arico M, Egeler RM, et al.: HLH-94: A treatment protocol for hemophagocytic lymphohistiocytosis. Med Pediatr Oncol, in press.
52. Marmaduke DP, Rosai R, Warnke R, Foucar K, Emmert-Buck MR, Liotta LA, Willman CL: Molecular assessment of clonality in sinus histiocytosis with massive lymphadenopathy (SHML): A reactive disorder of polyclonal histiocytes. Lab Invest 74:117A, 1996.
53. Foucar E, Rosai J, Dorfman RF: Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): Review of the entity. Semin Diagn Pathol 7:19–73, 1990.
54. Paulli M, Feller AC, Boveri E, Kindl S, Berti E, Rosso R, Merz H, Facchetti F, Gambini C, Bonetti F, Geerts ML, Moller P, Magrini U, Samloff M, Solcia E: Cathepsin D and E co-expression in sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) and Langerhans' cell histiocytosis: Further evidence of a phenotypic overlap between these histiocytic disorders. Virchows Archiv 424:601–606, 1994.
55. Peterson L, Dehner LP, Brunning RD: Extramedullary masses as presenting features of acute monoblastic leukemia. Am J Clin Pathol 75:140–145, 1981.
56. Lauritzen A, Ralfkiaer E: Histiocytic Sarcoma. Leuk Lymphoma 18:73–80, 1995.
57. Lennert K, Feller AC, Radzun HJ: Malignant histiocytosis/histiocytic sarcoma and related neoplasms. Rec Adv in RES Res 24:1–16, 1984.
58. Wilson MS, Weiss LM, Gatter KC, Mason DY, Dorfman RF, Warnke RA: Malignant histiocytosis. A reassessment of cases previously reported in 1975 based on paraffin section immunophenotyping studies. Cancer 66:530–536, 1990.
59. Egeler RM, Schmitz L, Sonneveld P, Mannival C, Nesbit ME: Malignant histiocytosis: A reassessment of cases formerly classified as histiocytic neoplasms and review of the literature. Med Ped Oncol 25:1–7, 1995.
60. Kaneko T, Fukuda J, Yoshihara T, Zheng H, Mori S, Mizoguchi H, Oshimi K: Nasal natural killer (NK) cell lymphoma: Report of a case with activated NK cells containing Epstein-Barr virus and expressing CD21 antigen, and comparative studies of their phenotype and cytotoxicity with normal NK cells. Brit J Haematol 91:355–361, 1995.
61. Levine EG, Hanson CA, Jaszez W, Peterson BA: True histiocytic lymphoma. Semin Oncol 18:39–45, 1991.
62. Kamel OW, Gocke CD, Kell DL, Cleary ML, Warnke RA: True histiocytic lymphoma: A study of 12 cases based on current definition. Leuk Lymphoma 18:81–93, 1995.

63. Bucsky P, Favara B, Feller AC, Nezelof C, Radzun H, Schlegelberger B and Janka-Schaub G: Malignant Histiocytosis and Large Cell Anaplastic (Ki-1) Lymphoma in Childhood: Guidelines for Differential Diagnosis. Report from the Histiocyte Society. Med & Pediatr Oncol 22:200–203, 1994.
64. Orscheschek K, Merz H, Hell J, Binder T, Bartels H, Feller AC: Large-cell anaplastic lymphoma-specific translocation (t[2;5] [p23;q35]) in Hodgkin's disease: Indication of a common pathogenesis? Lancet 345:87–90, 1995.
65. Wellmann A, Otsuki T, Vogelbruch M, Clark HM, Jaffe ES, Raffeld M: Analysis of the t(2;5)(p23;q35) translocation by reverse transcription-polymerase chain reaction in CD30+ anaplastic large-cell lymphomas, in other non-Hodgkin's lymphomas of T-cell phenotype and in Hodgkin's disease. Blood 86:2321–2328, 1995.
66. Arber DA, Sun L-H, Weiss LM: Detection of the t(2;5)(p23;q35) chromosomal translocation in large B-cell lymphomas other than anaplastic large cell lymphoma. Hum Pathol 27:590–594, 1996.